Support for the amendments to claims 28 and 30 may be found in the specification at page 15, lines 39-41 and in Figure 2.

Amended claim 31 is supported by Figures 1-2 of the specification.

A substitute Declaration will be submitted to obviate the Examiner's objection at page 2 of the Office Action.

Applicant notes that there are no outstanding rejections for claims 6 and 24. Therefore, claims 6 and 24 are allowable.

The 35 U.S.C. § 112, second paragraph, rejection

The Examiner rejected claims 28 and 30 under 35 U.S.C. § 112, second paragraph. The amendments to the claims render this rejection moot. Therefore, withdrawal of the rejection of the claims under § 112, second paragraph, is respectfully requested.

The 35 U.S.C. § 112, first paragraph, rejections

The Examiner rejected claim 26 under 35 U.S.C. § 112, first paragraph, alleging that there is no guidance or examples pertaining to the use of an H4-1BB polypeptide in the specification that would provide a reasonable expectation of success of using the claimed invention to treat a T cell-associated disease or clinical condition. In addition, the Examiner rejected claims 5 and 26-31 under 35 U.S.C. § 112, first paragraph, asserting that those claims encompass subject matter which was not disclosed in the specification. As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

Claim 26 is directed to a composition comprising a purified soluble H4-1BB polypeptide which comprises the extracellular domain (ECD) of SEQ ID NO:2, or a fragment of the ECD, in admixture with a suitable diluent, carrier or excipient. It is disclosed that H4-1BB, e.g., a soluble form thereof, may be employed to raise antibodies thereto (page 16, lines 36-37). Figures 4(b)-(c) and 5(b)-(c) of the specification also illustrate the interaction of 4-1BB on T cells with its ligand on antigen presenting cells, and how 4-1BB can be used to suppress T cell-dependent immune responses. Note that Figures 3-5 also show other molecules on antigen presenting cells and their respective ligands on T cells. Since 4-1BB is induced during T cell activation (page 5, lines 30-

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32), a polypeptide such as that recited in claim 24 can block the interaction of T cells with antigen presenting cells which express H4-1BB ligand, thereby resulting in immunosuppression. Thus, a fusion protein comprising the ECD of H4-1BB can have an immunosuppressive effect (page 17, line 37-page 18, line 3).

To provide further evidence that the specification, in view of the knowledge of the art worker in the relevant art area, would provide the art worker with a reasonable expectation in that the claimed composition would be useful to treat undesirable T cell-mediated immune responses, the Examiner is requested to reconsider Linsley et al. (Science, 257, 792 (1992) (of record)), in view ofTurka et al. (Proc. Natl. Acad. Sci. U.S.A., 89, 11102 (1992)), and Gimmi et al. (Proc. Natl. Acad. Sci. U.S.A., 90, 6586 (1993)) (a copy of the latter two articles is enclosed herewith).

Linsley et al. disclose that B7 is a molecule on antigen presenting cells that binds to T cell surface molecules CD28 and CTLA-4 (see also Figures 4(a)-(b) and 5(a)-(b) of the specification). The binding of B7 on B cells to CD28 or CTLA-4 on T cells activates T cells. A soluble fusion protein having the extracellular domain of CTLA-4 and Ig suppressed T cell-dependent antibody responses *in vivo* after mice were injected with one of two different antigens.

Turka et al. disclose that the cardiac allografts of animals treated with daily injections of the CTLA4-Ig fusion protein remained functional, while untreated animals and animals treated with a control antibody uniformly rejected their grafts (page 11103, second column). Turka et al. also found that the significant increase in the survival of cardiac allograft in rats treated with the CTLA4-Ig fusion protein was the result of the blocking of the B7/CD28 activation of T cells (page 11105). Gimmi et al. comment on the clinical utility of the inhibition of the B7/CD28 costimulatory pathway in the induction of tolerance in humans (abstract).

In view of Applicant's disclosure and the knowledge possessed by one of ordinary skill in the relevant art, as evidenced by the above-mentioned references, one of ordinary skill in the art would reasonably expect that the binding of a soluble form of H4-1BB to the ligand for H4-1BB on antigen presenting cells would suppress T cell-dependent responses, and so would be useful to suppress or block T cell activation *in vivo*.

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With respect to the rejection of claims 5 and 26-31, the Examiner alleges that: 1) claims 5 and 26-31 read on a gene, or an entire chromosome, and that the specification does not particularly describe elements including regulatory elements and untranslated regions which are essential to the function of the claimed invention, 2) there is no known or disclosed correlation between the function and the structure of the non-described regulatory elements and untranslated region of the gene, and 3) there is no additional disclosure of physical and/or chemical properties, and so one of skill in the art would not recognize from the disclosure that Applicant was in possession of the genus of genes which encodes SEQ ID NO:2.

To satisfy the written description requirement of §112(1), the description of the invention must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. Univ. of Calif. v. Eli Lilly and Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997). Figure 2 of the specification discloses a nucleic acid sequence, i.e., SEQ ID NO:1, which encodes a H4-1BB protein having SEQ ID NO:2. It is further disclosed that cDNAs encoding SEQ ID NO:2 were obtained by using two primer pairs to amplify human sequences that are related to murine 4-1BB. The specification also discloses the introduction of an expression vector containing a DNA comprising SEQ ID NO:1 into a cell results in the recombinant expression of an encoded protein, e.g., SEQ ID NO:2 or a fragment thereof (page 4, lines 29-34 and page 16, lines 4-21). For instance, Applicant discloses that vectors for expression in insect cells (page 13, lines 10-15) or mammalian cells (i.e., Aptaq-1, page 16, line 12) may be used for the recombinant production of proteins of the present invention. At page 15, a vector encoding a soluble H4-1BB fusion protein is described.

Claim 5 is directed to a H4-1BB protein produced by recombinant means, i.e., an expression vector comprising a DNA which encodes a protein having SEQ ID NO:2 or a soluble fragment thereof is introduced to a host cell and the encoded protein is expressed. Claims 27-29 are directed to a soluble H4-1BB protein produced by recombinant means. Claim 26 is directed to a composition comprising a soluble H4-1BB polypeptide which comprises the ECD of SEQ ID NO:2 or a fragment thereof. Claims 30-31 are directed to a soluble H4-1BB polypeptide which comprises the ECD of SEQ ID NO:2 or a fragment thereof, which polypeptide is encoded by a certain DNA sequence or which comprises amino acid residues 1-186 of SEQ ID NO:2.

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Claims 5 and 27-29 recite that the H4-1BB polypeptide is expressed from an expression cassette which is introduced into a host cell. Therefore, claims 5 and 27-29 do not read on a gene or an entire chromosome. As claims 26 and 30-31 are directed to a purified soluble H4-1BB polypeptide comprising the ECD of SEQ ID NO:2 or a fragment thereof, it is unclear to Applicant's Representatives how these claims read on a gene or an entire chromosome, or lack a description of regulatory elements or untranscribed regions. Further clarification is respectfully requested.

It is well known to the art worker that: i) DNAs which have a silent mutation(s) in an open reading frame encode the same polypeptide as a DNA without the mutation, and ii) expression vectors often include regulatory elements some of which can direct or enhance basal levels of transcription, e.g., promoters or enhancers, from linked DNA sequences, and that many such regulatory elements can be employed to express any particular linked DNA sequence.

Given that Applicant has described a DNA which encodes SEQ ID NO:2, i.e., SEQ ID NO:1, one of ordinary skill in the art would recognize that Applicant was in possession of the genus of DNAs that encode SEQ ID NO:2. Further, because the essence of the invention does not lie within a particular regulatory element or untranslated region, Applicant should be entitled to designate these variables in terms sufficiently broad to afford protection of his invention against easy circumvention. Ex parte Dubbs and Stevens, 119 U.S.P.Q. 440 (Bd. App. 1958).

Thus, it is Applicant's position that the invention of claims 5 and 26-31 is adequately described in the specification, and that one of ordinary skill in the art in possession of Applicant's disclosure would recognize that the inventor had possession of the claimed invention at the time of filing.

Therefore, withdrawal of the 35 U.S.C. § 112, first paragraph, rejections is respectfully requested.

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Conclusion

Applicant believes the claims are in condition for allowance and request reconsideration of the application and allowance of the claims. The Examiner is invited to telephone the below-signed attorney at 612-373-6959 to discuss any questions which may remain with respect to the present application.

Respectfully submitted,

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Date October 27, 2000 By _____
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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner of Patents, Washington, D.C. 20231 on **October 27, 2000**.

Dawn M. Poole
Name

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Signature

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